IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of	:	**Confirmation No. 7559**
Ryouichi HOSHINO et al.	:	Attorney Docket No. 2006_0019A
Serial No. 10/566,503	:	Group Art Unit 1618
Filed February 6, 2006	:	Examiner Nissa M. Westerberg
ORAL-SUSTAINED-RELEASE TABLET	:	**Mail Stop: RCE**

DECLARATION UNDER 37 CFR 1.132

Commissioner for Patents,

Alexandria, VA

Sir:

I, Yasuhiro Yamamoto, the undersigned, a citizen of Japan, residing at 186-26 Shinmei-Cho 2 Chome, Koshigaya-Shi, SAITAMA 343-0805 JAPAN, do hereby declare:

1. That I am employed in the Chemical Process & Pharmaceutics Division of Development Research Laboratories of Kyorin Pharmauceutical Co., Ltd., the assignee of the present application.

2. That I graduated from Tokyo University of Science on March 31, 1996 with a master's degree in Medical and Pharmaceutical Science.

3. I have consistently pursed pharmaceutical formulation study as a researcher.

I, Yoshikazu Miyazaki, the undersigned, a citizen of Japan, residing at 220, kyorin Tomonuma-Ryou, 6095, Nogi-machi, Shimotsuga-gun, TOCHIGI 329-0101 JAPAN, do hereby declare:

1. That I am employed in the Chemical Process & Pharmaceutics Division of Development Research Laboratories of Kyorin Pharmauceutical Co., Ltd., the assignee of the present application.

2. That I graduated from Osaka Prefecture University on March 31, 2008 with a master's degree in Chemical Engineering.

I. Purpose of the Declaration

This Declaration is provided to demonstrate and clarify the difference between the high-viscosity hydroxypropylmethylcellulose (HPMC-HV, being a sustained-release base) used in the present invention, and the low-viscosity HPMC (HPMC-LV, being a coating base) used in the KRP-197 preparation patent, (WO 01034147, filed by Ohyama et al. of Kyorin Pharmaceutical Co., Ltd., hereafter referred to as the "Ohyama patent"). The following discussion supports the assertion that the invention set forth in U.S. Application No. 10/566,503 is not obvious based on the teachings of EP 1245232 (corresponds to WO 01034147).

We have conducted experiments to confirm that the HPMC-HV cannot be used as a coating base using the method described in the Ohyama patent. Furthermore, even if the HPMC-HV can be used as a coating base, sustained-releasability cannot be expected. Thus, these experiments clarify the difference between the HPMC-HV of the present invention, and the HPMC-LV used by Ohyama et al.

These experiments were performed from February 4, 2009 to February 16, 2009.

II. Experiments

A Uritos tablet (uncoated tablet weight of 0.1 mg), made in accordance with the description shown in Table 1 herein, was coated with HPMC-LV (trade name "TC-5", Shin-Etsu Chemical Co., Ltd.) or HPMC-HV (trade name "Metlose 60SH-4000", Shin-Etsu Chemical Co., Ltd.) using the method described in the Ohyama patent under the coating condition detailed in Table 2 herein. The HPMC-LV in 2% aqueous solution has a viscosity of 3-15 cps at 20°C, while the HPMC-HV in 2% aqueous solution has a viscosity of 4000 cps at 20°C.

Additionally, disintegration tests were performed for six tablets coated with HPMC-HV or HPMC-LV. The tests were carried out in water as a test liquid according to the procedure described in the Japanese Pharmacopoeia (15th revised edition).

III. Discussion of interpreting results

It was determined that a coating failure occurred when: (1) it is impossible to spray the coating liquid on the uncoated tablet, (2) the spray-coated tablets are adhered to each other, or (3) there is any trace of adherence found.

It was determined that the coating-process efficiency (of HPMC-HV) had deteriorated when the coating time required was at least twice as long as the coating time for HPMC-LV.

When coating failure and/or coating-efficiency deterioration was observed, it was determined that the method of the Ohyama patent could not be employed with a coating of HPMC-HV.

When the tablets completely disintegrated within 60 minutes, it was determined that sustained releasability could not be expected.

IV. Test Results

Suitability as a coating base

An 8% HPMC-LV aqueous solution was sprayed on an uncoated tablet, and there were no aggregations of coated tablets. Accordingly, it was determined that there was no coating failure. (Please see Table 2, Trial No. 1.)

On the other hand, an 8% HPMC-HV aqueous solution had a significantly high viscosity so that the solution contained in a preparation tank was hardly moved even when the tank was slanted. (Please see Figure 1.) As the solution could not be sucked using a pump, spraying on an uncoated tablet could not be achieved. (Please see Table 2, Trial No. 2.)

In order to properly suck the solution using a pump, a 1.6% HPMC-HV aqueous solution was prepared so as to have a suitable viscosity for suction, and the solution was sprayed on an uncoated tablet with a high pressure so that the sprayed liquid particle had a small diameter for suppression of the adherence between the coated tablets. (Please see Table 2, Trial No. 3.) It was confirmed that the liquid spraying was successfully performed, but the adherence between the coated tablets, adherence trace, and adherence onto a coating pan were found. (Please see Figure 2.) Furthermore, the coating time required was at least four times as long as the coating time required in Trial No. 1 (for HPMC-LV).

In conclusion, when HPMC-HV was coated on an uncoated tablet using the method of the Ohyama patent, coating failure occurred and the coating-process efficiency significantly deteriorated. Therefore, it is determined that HPMC-HV cannot be used as a coating base.

Sustained releasability of the coated tablet

The tablet coated with an 8% HPMC-LV aqueous solution (Trial No. 1) was completely disintegrated within 90 seconds. This result is clearly outside the rough standard of sustained releaseability, which requires that the time for disintegration be 60 minutes or more. As described in the test example of WO 2005/011682 (the publication of the international application, upon which the present application is based), it is determined that sufficient sustained releasability is not expected.

The tablet coated with a 1.6% HPMC-HV aqueous solution (Trial No. 3) was completely disintegrated within 12 minutes. Again, this falls outside the rough standard of sustained releaseability. Accordingly, it is determined that sufficient sustained releaseability is not expected.

The tablets prepared in accordance with the method described in Examples 4, 5, and 6 of WO 2005/011682 (with regard to KRP-197 sustained release tablets) were examined in the same manner as in the previous disintegration tests. It was observed that the tablet of Example 6 swelled better than the table of Example 5, which swelled better than the table of Example 4. Furthermore, it was observed that the tablet of Example 4, which contains less amount of HPMC-LV, was disintegrated slowly from the outer layer thereof. However, none of the tablets were completely disintegrated over three hours. Thus, each of these tablets show sufficient sustained releasability.

V. Conclusion

As described above, it is not possible to coat an uncoated tablet with HPMC-HV using the method described in the Ohyama patent, unless the viscosity is affected. Even if a tablet is coated with HPMC-HV using the Ohyama method, sustained releaseabiilty is not expected. Accordingly, the HPMC-LV used in the Ohyama patent is determined to be quite different from the HPMC-HV.

Table 1: Description of uncoated Uritos tablet (0.1 mg) [a)]

Component	Function	Content (mg)
Imidafenacin	Active ingredient	0.1
Crystallized cellulose	Excipient	105.7
Partly gelatinized starch	Excipient	26.4
Povidon	Binder	1.4
Magnesium Stearate	Lubricant	0.4
Total:		**134**

a) : product of Kyorin Pharmaceutical Co., Ltd, Noshiro factory (lot number K003).

Table 2: Coating conditions

Equipment and Conditions	Trial No.		
	1 [b)]	2 [c)]	3 [d)]
Equipment	High Coater Mini	High Coater Mini	High Coater Mini
Number of charged uncoated tablets	2000	2000	2000
Liquid amount (g)	125	125	625
Rate (g/min)	2	-	2
Pressure (kgf/cm^2)	1.0	1.0	1.5
Fed air temperature (°C)	60-73	-	62-72
Time (min)	63	-	304

b) : using 8% HPMC-LV aqueous solution for coating

c) : using 8% HPMC-HV aqueous solution for coating

d) : using 1.6% HPMC-HV aqueous solution for coating

- : the solution cannot be sprayed for coating

Figure 1: Observation of viscous 8% HPMC-HV aqueous solution

Figure 2: tablet coated with 1.6% HPMC-HV aqueous solution

I further declare that all statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

Date: April 21, 2009

Yasuhiro Yamamoto
(Signature of Declarant)

Yasuhiro Yamamoto

I further declare that all statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

Date: April 21, 2009

Yoshikazu Miyazaki
(Signature of Declarant)

Yoshikazu Miyazaki